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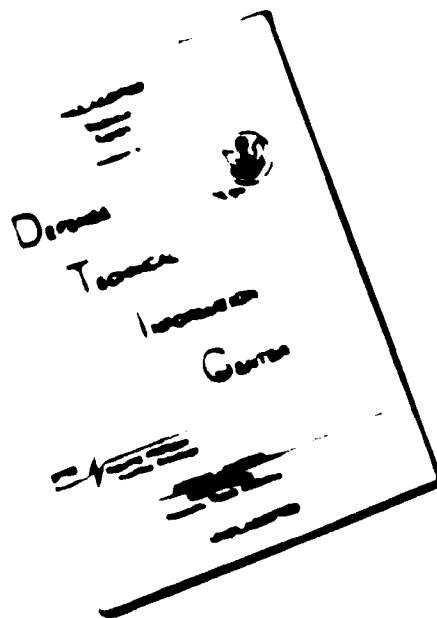
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## Human T Cell Lymphotropic Virus Type I Infection among Female Sex Workers in Peru

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Four hundred female sex workers attending a sexually transmitted disease clinic in Lima, Peru, were interviewed for demographic information and medical, contraceptive, and sexual practice histories. Cervical cultures were done for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, and serum was tested for antibodies to human immunodeficiency virus, human T cell lymphotropic virus type I (HTLV-I), *Treponema pallidum*, *C. trachomatis*, herpes simplex virus type 2 (HSV-2), and *Haemophilus ducreyi*. The prevalence of HTLV-I increased with duration of prostitution from 3.6% (<3 years) to 9.3% (3–6 years) to 15.9% (>6 years;  $P < .01$ ). After adjustment for duration of prostitution, reduced risk of HTLV-I was significantly correlated with condom use for more than half of all sexual exposures for >3 years (odds ratio [OR], 0.34; 95% confidence interval [CI], 0.13–0.89). Further adjusting for condom use, HTLV-I seropositivity was associated with *C. trachomatis* (OR, 3.7; 95% CI, 1.4–13.2) and with antibody to HSV-2 (OR, 3.7; 95% CI, 0.5–29.5). Thus, duration of prostitution, lack of consistent condom use, and past infection with *C. trachomatis* were significantly associated with HTLV-I seropositivity.

Human T cell lymphotropic virus type I (HTLV-I) is associated with a variety of clinical syndromes, including adult T cell leukemia/lymphoma [1, 2] and HTLV-associated human myelopathy/tropical spastic paraparesis [3]. The virus is endemic in southwestern Japan [1], the southeastern United States [4], the Caribbean basin [5], South America [6, 7], and parts of Africa [8]. Patterns of age- and sex-specific prevalence of HTLV-I differ from country to country, suggesting different dynamics of transmission [9]. The major routes of transmission are from mother to child via breast-feeding [10, 11], through blood transfusion [12], and via sexual transmission [13]. Among Japanese married couples, concordant seropositivity is much more common than expected by chance; transmission from man to woman is more common than from woman to man, and risk factors for transmission within

serologically discordant couples include older age, high antibody titers, and presence of anti-*sax* antibody in the seropositive male spouses [13, 14]. In South America, recent information suggests that HTLV-I may be common in groups at risk for sexually transmitted diseases (STD). Including human immunodeficiency virus (HIV) infection [6, 7]. Data regarding the risk factors for sexual transmission are limited and contradictory, although preliminary data suggest an analogy to risk factors for sexual transmission of HIV [15–17]. The present study assesses the relationship of HTLV-I infection to sexual behavior and demographic variables and to STDs (including HIV infection) among female sex workers (FSW) attending an STD clinic in Lima, Peru.

### Methods

**Study population and design.** A cross-sectional survey of the epidemiology of HTLV-I was done among FSW in Lima between October 1991 and April 1992. Study participants attended the Centro Antivénereo de Lima, an STD clinic that provides regular health care to FSW. This clinic primarily serves a population of FSW who present for health examinations every 15 days to renew their health registration card required for them to work within the legal prostitution system. Participants were interviewed for demographic information and medical, obstetric, contraceptive, sexual practices, and prostitution histories. Genital examination included cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. After pretest counseling, 30 mL of venous blood was obtained for serologic tests for syphilis and were later assayed for antibodies to HIV, HTLV-I, *C. trachomatis*, herpes simplex virus type 2 (HSV-2), and *Haemophilus ducreyi*.

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Informed consent was obtained from participants, and the research protocol was approved by the Human Subject Review Committee of the University of Washington and the Scientific Research Office at the Universidad Peruana Cayetano Heredia.

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**Laboratory methods.** HTLV-I antibodies were determined by ELISA (Genetic Systems, Seattle), and persistently reactive sera were tested by Western blot (Cambridge Biotech, Worcester, MA). Sera were considered positive if antibodies to p24, p19, and gp46 proteins were demonstrated and intensity of reactivity to the p19 band was greater than that of the p24 band; samples were classified as negative if none of the diagnostic bands appeared; any other band patterns were regarded as indeterminate [18, 19]. Culture assays for *N. gonorrhoeae* and *C. trachomatis* were done as previously described [20, 21]. Tests for antibodies to HIV were done by ELISA (Abbott Laboratories, Abbott Park, IL) and confirmed by Western blot (Cambridge Biotech) according to World Health Organization criteria [18]. Sera were tested for *Treponema pallidum* antibody by the fluorescent treponemal antibody absorption test (Difco, Detroit) [22]. The microimmunofluorescence assay [21] was used to test sera for antibodies to *C. trachomatis*; antibody titers of  $\geq 1:16$  were considered evidence of past infection. Sera were tested for HSV-2 antibody by Western blot assay [23] and for antibody to *H. ducreyi* by ELISA [24].

**Data analysis.** Univariate analyses were done for selected variables using the  $\chi^2$  test, the Mantel-Haenszel test for linear trend, and Student's *t* test. Odds ratios (ORs) were used to estimate relative risks. Stepwise logistic regression (SPSS/PC 4.01 program; SPSS, Chicago) assessed the relationship between HTLV-I infection and selected risk factors. Factors with  $P < .2$  in the univariate analyses were entered into the model; variables were included in the final model if they increased significantly ( $P < .05$ ) the predictive power of the model. Association between current or past evidence of STD and HTLV-I was adjusted for possible confounders using logistic regression analysis.

## Results

Participants were 400 FSW (284 registered for routine periodic examination with the Centro Antivenéreo of the Ministry of Health and 116 not registered). The mean age was  $28.8 \pm 6.4$  years (range, 18–48). Overall, 28 (7%) were confirmed seropositive for HTLV-I. Sera from 4 women were positive by ELISA and indeterminate by Western blot assay. Three of the 4 with indeterminate results had the p21 env band and could be considered positive according to the investigational Western blot (Cambridge Biotech). However, to be conservative, all 4 indeterminates were excluded from further analysis, as further research experience will be necessary to determine the specificity and sensitivity of these criteria [25].

The prevalences by culture were 7.5% for *N. gonorrhoeae* (30/390) and 13.8% for *C. trachomatis* (55/398). The overall seroprevalences of antibodies were as follows: *T. pallidum*, 19% (76/400); *C. trachomatis*, 55.8% (223/400); HSV-2, 82.2% (328/399); and *H. ducreyi*, 27% (108/400).

Table 1 compares the HTLV-I seropositive and -negative groups for selected demographic and medical history variables. Increasing age and decreasing education level corre-

**Table 1.** Univariate analysis of the relationship of sociodemographic and medical history characteristics to HTLV-I infection among female sex workers (FSW) in Lima.

	No. positive for HTLV-I/total (%)	Odds ratio (95% CI)
<b>Age (years)*</b>		
<21	0/37	
21–25	3/107 (2.8)	1.0
26–30	9/120 (7.5)	3.8 (1.7–8.6) <sup>†</sup>
>31	16/131 (12.2)	6.5 (2.9–14.6) <sup>†</sup>
<b>Education**</b>		
Elementary	7/59 (11.9)	1.0
High school	19/238 (8.0)	0.6 (0.3–1.3)
University/technical	2/97 (2.1)	0.2 (0.1–0.4)
<b>Marital status</b>		
Single	12/213 (5.6)	1.0
Cohabitant/ever married	16/182 (8.8)	1.6 (0.7–3.5)
<b>Place of birth</b>		
Coast	17/296 (5.7)	1.0
Highlands	6/54 (11.1)	2.1 (0.6–5.8)
Jungle	4/45 (8.9)	1.6 (0.4–5.2)
<b>Occupation other than FSW</b>		
No	20/249 (7.7)	1.0
Yes	8/144 (5.6)	0.7 (0.3–1.6)
<b>Blood transfusion</b>		
No	23/346 (6.6)	1.0
Yes	5/47 (10.6)	1.7 (0.6–4.9)
<b>Prophylactic penicillin injections*</b>		
No	12/243 (4.9)	1.0
Yes	16/152 (10.5)	2.3 (1.0–4.9)
<b>History of syphilis</b>		
No	22/344 (6.4)	1.0
Yes	6/43 (13.3)	2.3 (0.9–5.9)
<b>History of gonococcal infection</b>		
No	18/269 (6.7)	1.0
Yes	10/119 (8.4)	1.3 (0.6–2.9)

NOTE. CI, confidence interval.

\*  $\chi^2$  test;  $P < .05$ .

<sup>†</sup> Mantel-Haenszel test for linear trend;  $P < .05$ .

<sup>‡</sup> Reference category: FSW  $\leq 25$  years old.

lated significantly with increasing prevalence of HTLV-I antibodies. Women who ever received prophylactic penicillin G benzathine injections (frequently used in Peru to prevent or abort syphilis among FSW) had a higher prevalence of HTLV-I antibodies than other women ( $P < .05$ ). HTLV-I seropositivity was present in 6 (13.3%) of 45 women who had a history of syphilis, compared with 22 (6.4%) of 344 who did not report a history of syphilis ( $P = .12$ ). Marital status, place of birth, occupation other than prostitution, history of blood transfusion, history of gonococcal infection, and history of tattoos or acupuncture were not significantly associated with HTLV-I. None of the 400 women acknowledged ever having used intravenous drugs.

Univariate analyses of sexual behavior and details of the practice of prostitution in relation to HTLV-I infection are shown in table 2. Time working as an FSW and condom use

**Table 2.** Univariate analysis of the relationship of sexual behavior and practice of prostitution characteristics to HTLV-I infection among female sex workers (FSW) in Lima.

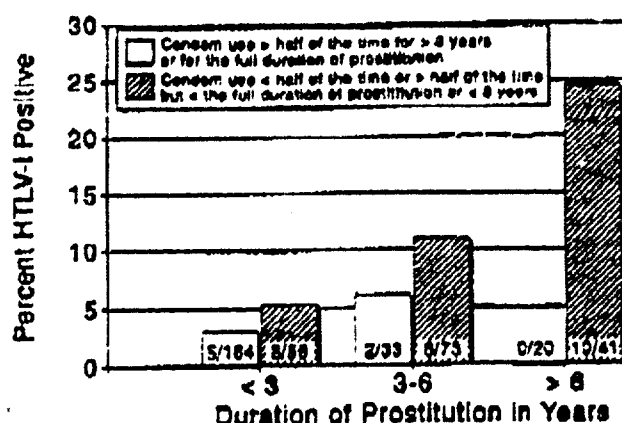
	No. positive for HTLV-I/total (%)	Odds ratio (95% CI)
<b>Age at first sexual intercourse (years)</b>		
>18	2/71 (2.8)	1.0
14-18	22/291 (7.6)	2.8 (0.7-25.3)
<14	3/31 (9.7)	3.7 (0.6-45.8)
<b>Years working as FSW<sup>a</sup></b>		
<3	8/225 (3.6)	1.0
3-6	10/108 (9.3)	2.8 (1.0-8.0)
>6	10/63 (15.9)	5.1 (1.8-15.1)
<b>Clients/day</b>		
<6	19/288 (6.6)	1.0
6-10	7/82 (8.5)	1.3 (0.5-3.4)
>11	2/20 (10.0)	1.6 (0.2-7.4)
<b>Registered FSW</b>		
No	8/116 (6.9)	1.0
Yes	20/280 (7.1)	1.0 (0.4-2.7)
<b>Socioeconomic status of the client</b>		
High	9/162 (5.6)	1.0
Medium	8/110 (7.3)	1.3 (0.5-3.9)
Low	11/120 (9.2)	1.7 (0.6-4.7)
<b>Ever work out of Lima</b>		
No	21/312 (6.7)	1.0
Yes	7/83 (8.4)	1.3 (0.5-3.1)
<b>Alcohol before sex last year</b>		
No	13/218 (6.9)	1.0
<1/2 of the time	9/124 (7.3)	1.1 (0.4-2.7)
>1/2 of the time	4/49 (8.2)	1.2 (0.3-4.0)
<b>Drugs before sex</b>		
No	23/337 (6.8)	1.0
Yes	3/51 (9.8)	1.5 (0.5-4.1)
<b>Sex during menses</b>		
No	10/113 (8.8)	1.0
<1/2 of the time	13/227 (5.7)	0.6 (0.3-1.6)
>1/2 of the time	3/55 (9.1)	1.0 (0.3-3.5)
<b>Anal sex</b>		
No	11/172 (6.4)	1.0
Seldom	10/152 (6.6)	1.0 (0.4-2.7)
More often	7/68 (10.6)	1.7 (0.6-5.1)
<b>Performed oral sex</b>		
No	3/83 (3.6)	1.0
Yes	25/307 (8.1)	2.4 (0.7-8.0)
<b>Ever use oral contraceptives<sup>b</sup></b>		
No	4/115 (3.5)	1.0
Yes	24/272 (8.8)	2.7 (0.9-7.9)
<b>Condom use with clients<sup>c</sup></b>		
<1/2 of the time, or >1/2 of the time but less than the full duration of prostitution or <3 years	21/170 (12.4)	1.0
>1/2 of the time for >3 years or for full duration of prostitution if <3 years	7/200 (3.5%)	0.24 (0.1-0.6)

NOTE. CI, confidence interval.

<sup>a</sup>  $\chi^2$  test;  $P < .05$ .

<sup>b</sup> Mantel-Haenszel test for linear trend;  $P < .05$ .

<sup>c</sup>  $\chi^2$  test;  $P = .06$ .



**Figure 1.** Seroprevalence of HTLV-I according to duration of prostitution and condom use.

more than half of the time for >3 years or for the full duration of prostitution if <3 years were significantly associated with antibodies to HTLV-I. There was also a trend toward an association of HTLV-I with history of oral contraceptive use (OR, 2.7; 95% confidence interval [CI], 0.9-7.9;  $P = .06$ ). The mean number of clients per day and type of sexual activity (e.g., sex during menses, receptive anal sex, and performance of oral sex) were not significantly associated with HTLV-I seropositivity.

The relationships between HTLV-I and all factors significant in the univariate analyses were further assessed by stepwise logistic regression analysis. In addition, a multiplicative interaction between age and duration of work as an FSW was used as a variable. The use of condoms more than half of the time for >3 years or for the full duration of prostitution and duration of prostitution entered the model. After these variables entered the model, the other potential demographic and behavioral variables were no longer associated with HTLV-I infection. The above variable for condom use was independently associated with HTLV-I, even after adjusting for time working as an FSW (OR, 0.34; 95% CI, 0.13-0.89;  $P < .05$ ). The relationship of HTLV-I seroprevalence to condom use for each stratum of duration of prostitution is shown in figure 1. Figure 1 suggests an interaction between the amount of condom use and duration of prostitution as predictors of the percentage HTLV-I positive. Adding an interaction term to the model with both main effects also suggests this possibility ( $P = .11$ ). In a stepwise run with variables significant in the univariate analysis (including both main effects) and the interaction term, the interaction term was the first term to enter the model ( $P = .004$ ), followed by condom use ( $P = .02$ ); no other variables entered.

The association of HTLV-I to current and past STDs were next examined by univariate analyses. HTLV-I seropositivity was found in 6 (11.1%) of 54 with and in 21 (6.2%) of 340 without current chlamydial infection (OR, 1.9; 95% CI, 0.6-

Table 3. Serologic evidence of sexually transmitted diseases as risk factors for HTLV-I.

	No. positive for HTLV-I/total (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	P
<i>Treponema pallidum</i>				
No	21/320 (6.5)	1.0		
Yes	7/75 (9.3)	1.5 (0.6-3.6)	0.8 (0.3-2.2)	.74
<i>Chlamydia trachomatis</i>				
No	4/167 (2.4)	1.0		
Yes	22/220 (10.0)	4.5 (1.3-13.4)	3.8 (1.3-11.3)	.02
<i>Herpes simplex virus type 2</i>				
No	1/70 (1.4)	1.0		
Yes	27/325 (8.3)	6.3 (1.0-259.6)	3.7 (0.5-28.4)	.21
<i>Haemophilus ducreyi</i>				
No	19/310 (6.1)	1.0		
Yes	9/81 (11.1)	1.9 (0.8-4.4)	1.2 (0.5-2.8)	.67

NOTE. OR, odds ratio; CI, confidence interval.

\* Adjusted for duration of prostitution and condom use.

5.2;  $P = .18$ ) and in 0 of 29 with and 27 (7.4%) of 364 without gonorrhea ( $P = .2$ ).

The relationships between serologic evidence of STDs and HTLV-I are shown in table 3. Past infection with *C. trachomatis* and HSV-2 were strongly associated with HTLV-I seropositivity. Only 3 of 400 women were HIV-1-positive, none of whom had HTLV-I infection.

Finally, the relationship of serologic evidence of STD to HTLV-I seropositivity was assessed by logistic regression analysis, adjusting for time working as an FSW and condom use. This analysis showed that *C. trachomatis* antibody remained significantly associated with HTLV-I (table 3). The OR for antibody to HTLV-I with antibody to HSV-2 was also increased (OR 3.7), but this association was not statistically significant.

## Discussion

This study showed that HTLV-I was prevalent among FSW in Lima during 1992 and was nine times more prevalent than HIV. The association of HTLV-I infection with duration of prostitution and lack of condom use suggests that HTLV-I is acquired sexually in this population and that condom use is protective. The interaction effect between condom use and duration of prostitution is also consistent with the persistent effect of condom use.

Even after adjustment for duration of prostitution and condom use, HTLV-I infection was significantly associated with serologic evidence of past infection with *C. trachomatis* and not significantly with serologic evidence of HSV-2 infection. It is not clear why antibodies to *C. trachomatis* and HSV-2 were associated with increased ORs for HTLV-I in the adjusted analyses, while antibodies to *T. pallidum* and *H. ducreyi* were not associated. The serology test for *H. ducreyi* antibody is experimental and may have been relatively non-specific in this population. For syphilis, the frequency of ex-

amination may actually shorten the duration of infection, thereby decreasing or eliminating the role of this exposure as a risk factor. Of course, it remains possible that exposures to *C. trachomatis* and HSV-2 were only markers for sexual exposure to HTLV-I, rather than true risk factors, despite efforts to adjust for duration of prostitution as a possible confounder and despite evidence that number of sexual exposures was not a risk factor.

These data suggest that genital chlamydial infection and genital herpes may be risk factors for sexual transmission of HTLV-I, as has been reported for sexual transmission of HIV. Previous studies involving sex workers in the United States [26] and Peru [27] also have found that the duration of prostitution was related to HTLV-I seropositivity. Lack of condom use and serologic evidence of prior HSV-2 or chlamydial infection were not examined as risk factors for HTLV-I infection in those two studies. However, other studies have suggested associations of HTLV-I infection with syphilis [15, 27, 28] and HSV-2 [16, 29]. Lack of a satisfactory serologic test for past gonococcal infection precluded an analysis of prior gonorrhea as a risk factor for HTLV-I infection.

The prevalence of HTLV-I among FSW in Lima was lower than that among FSW during 1988 in Callao (25%), the harbor of Lima [27]. However, the women in our study were younger ( $28.8 \pm 6.4$  vs.  $33.8 \pm 8.2$  years), had worked as prostitutes for fewer years ( $3.5 \pm 4.0$  vs.  $8.8 \pm 6.7$ ), and had had fewer clients per month ( $59 \pm 79$  vs.  $214 \pm 138$ ) than the women in Callao. Therefore, differences in total number of exposures may account for the difference in the prevalence between the two populations.

As reported for other HTLV-I-endemic populations, the prevalence of antibodies increased with age. Explanations previously postulated included a possible cohort effect (i.e., the probability of exposure in past years may have been greater than in recent years). However, in the multivariate

analysis, neither age nor the interaction between age and duration of prostitution had a significant influence on the model. Indicating that the duration of exposure as an FSW and lack of condom use, independent of age, were the important correlates for the acquisition of HTLV-I.

Sexual behavior risk factors have been implicated in other cross-sectional studies of HTLV-I infection. Number of sex partners has been associated with HTLV-I seropositivity in Jamaica [15], Trinidad [17], and the United States [26]. In the present study, an association was not observed, perhaps because of the large and highly variable number of clients and because our estimate of the number of recent clients may not have reflected the total number of lifetime exposures.

*C. trachomatis* produces an intense subepithelial mononuclear cell inflammatory response in the cervix and epithelial microulcerations. This mucosal disruption and inflammation could facilitate HTLV-I transmission in a manner analogous to that proposed for the effect of cervical chlamydial infection on HIV-I transmission in Africa [30, 31]. Alternatively, chlamydial urethritis might render a man with HTLV-I infection more infectious and more likely to transmit HTLV-I to a woman (along with chlamydia).

Although oral contraceptive use was associated with HTLV-I infection by univariate analysis, the association was not supported by the multivariate model. Nonetheless, oral contraceptive use increases the age-specific prevalence of cervical ectopy, and cervical ectopy may increase a woman's risk of acquiring HIV [32]. Two prospective studies in Nairobi found an association of oral contraceptive pill use with risk of HIV infection [30, 33], while other studies have found no such association [34, 35], leaving the question unresolved. The relationship of cervical ectopy to risk of acquisition of HTLV-I should be examined further.

Parenteral transmission does not appear to be a major route of acquisition of HTLV-I among FSW in Lima. Blood transfusion has not been associated with HTLV-I in this population, and parenteral drug use is uncommon in Peru. However, needles and syringes are commonly reused in Peru, and prophylactic injections of penicillin are commonly given to FSW. This could be a risk factor for HTLV-I transmission if the needles and syringes are improperly sterilized before reuse. However, in the multivariate analysis model, history of penicillin prophylaxis did not remain associated with HTLV-I infection.

Whereas perinatal transmission of HTLV-I or transmission through breast-feeding from mother to child appear to be common in HTLV-I-endemic areas of Japan, these appear to be uncommon among FSW in Peru, since the prevalence of infection was very low for those just beginning to work as FSW.

Our study is subject to several limitations. One was the inability to extrapolate to the entire population of FSW of Lima: our sample was biased toward FSW who attended the STD clinic regularly to renew their registration status and

who probably had better-than-average access to health care and STD treatment than did the FSW population as a whole. Furthermore, our cross-sectional study design did not definitively exclude cohort effects and could not directly infer incidence rates for HTLV-I infection. Further, the cross-sectional design did not permit assessment of the temporal relationship of other STDs to acquisition of HTLV-I or more quantitative assessment of the protective effect of regular condom use against HTLV-I infection. In addition, because other confirmatory tests could not be done on women positive for HTLV-I by ELISA and negative or indeterminate by Western blot, a small misclassification bias could have occurred. Nonetheless, the results of this study can serve as a guide for future prospective studies to further define risk factors for HTLV-I transmission and to assess the effectiveness of condom use for prevention of HTLV-I infection.

In summary, this study demonstrated that HTLV-I infection is common among FSW in Lima, that other STDs may increase risk of sexual acquisition of HTLV-I, and that condom use may be protective. The high prevalence of HTLV-I in older FSW is quite disconcerting, and surveys of other high-risk populations in Latin American are warranted. The significance of high rates of HTLV-I among FSW remains to be defined. The risk of transmission to clients and the risk of vertical transmission has not yet been studied in this population. What is the level of infectiousness at various times after acquisition of HTLV-I? Does the high risk of other STDs make FSW particularly likely to transmit HTLV-I? What is the risk of sequelae following adult acquisition of HTLV-I? Finally, what is the influence of HTLV-I on coexisting HIV infection in high-risk populations? Although these questions remain to be answered, there is reason to be concerned that HTLV-I infection may be an STD of major importance, at least in this region.

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